AMYOTROPHIC LATERAL SCLEROSIS

THE NEIGHBORHOOD IS BAD. SOME NEIGHBORS ARE DOWNRIGHT TOXIC, AND EVERYBODY ELSE SUFFERS FOR IT.

That's the situation with the degenerative disease amyotrophic lateral sclerosis, where cells in the neighborhood of motor neurons damage those neurons and cause a slow bodily degeneration. And it's leading researchers to focus on a community improvement campaign, said Don Cleveland, Ph.D., chair of cellular and molecular medicine at the University of California, San Diego School of Medicine. • The symptoms of ALS appear when motor neurons detach from the muscles they control. Once disconnected, the neurons die and the muscles waste. ALS patients lose the ability to do things for themselves: to walk, to speak and even to swallow. Eventually, the muscles that control breathing fail—the cause of most ALS deaths.

Although the roots of ALS are uncertain, three genetic mutations have been linked to it. But researchers had to determine just where the mutations did their dirty work. Were motor neurons damaged by their own genes, or was the damage caused by gene expression in neighboring cells?

Using rodents genetically engineered to develop ALS, researchers first shut off the ALS gene in the motor neurons, but kept it running everywhere else. As expected, the onset of disease was delayed, Cleveland said. But there was little meaningful improvement. "The speed by which the disease progresses is unchanged."

Then they reversed the experiment, keeping the gene going in the motor neurons, but shutting down its operation in its "intimate partner," the starburst-shaped astrocytes. In this case, symptom onset was unchanged, but the disease's progression slowed dramatically. It turns out astrocytes with the ALS mutation release a toxin that damages the motor neurons.

"In fact, the animals live more than twice as long," Cleveland said. The team hopes to replace mutant-expressing astrocytes with normal ones in ALS patients.

Life Technologies Corp. of Carlsbad, Calif., is growing embryonic stem cells and coaxing them to become astrocyte precursor cells that will then be injected into the spinal cords of ALS patients. That trial will begin within four years if animal trials succeed.

Researchers will inject the cells in either the lumbar or lower spine, where the leg muscles are innervated, or in the cervical spine (the neck), where motor neurons control breathing.

In preliminary animal studies, the astrocytic precursor cells survived and traveled along the spinal column, becoming astrocytes. Later trials will see if they spruce up the vicinity.

"What we learned is neighborhood really matters," Cleveland said.

"What kind of quality of life do you want, and what can you do to impact the quality? That's how I look at life."
DAN DESMOND

WHAT IS IT LIKE TO LIVE WITH ALS?

Dan Desmond caught himself using a hoe as a crutch as he walked his 6-acre property east of San Diego. It was one of the little hints he ignored until the day four years ago when he couldn't finish a hike. "My legs just weren't working," he said.

He had amyotrophic lateral sclerosis, the doctors told him, Lou Gehrig's disease. He went online to learn more and spent two hours at the ALS Association office in San Diego. "I did not like what I was hearing," he said. "I did not like the way things were going." But he found a way to cope.

"I still have a great life with my children, grandchildren and friends," the 64-year-old said. But the disease progresses. He's in a wheelchair. The muscles in his chest, arms and hands are growing weaker.

He subscribes to a philosophical attitude. "Everyone has depression at different times, and everybody's going to die at one time or another. So what we're talking about, from here to death, what kind of quality of life do you want, and what can you do to impact the quality? That's how I look at life."

He says he knows stem cell research underway today is not likely to help him, "but the research is going to help thousands of people down the road, and I think that's wonderful."